REMARKS/ARGUMENTS

Status of the Claims

Upon entry of the present amendment, claims 7 and 25-73 are pending. Claims 7 and 25-30 are amended. Claims 1-6 and 8-24 are canceled without disclaimer or prejudice to renewal. New claims 31-73 are added.

Claim 7 is amended to set forth a composition comprising a pVAX1 vector with specific modifications, as taught in Table 2. Support is found, for example, on page 15, lines 24-31 and in Figure 7; on page 39, line 26 through page 40, line 22; and on page 51, lines 1-20 and 23-24.

Claims 25-30 are amended to set forth an immune inhibitory nucleic sequence (IIS). Support is found, for example, on page 8, line 29 through page 9, line 5; on page 34, line 3 through page 35, line 21; and on page 39, line 26 through page 40, line 22.

New claims 31, 44 and 62 find support, for example, on page 12, lines 18-19; and on page 21, lines 12-14.

New claims 32, 51 and 69 find support, for example, in Table 1 on page 26, line 1 through page 27, line 2; and on page 28, lines 6-7.

New claims 33-34, 52-53 and 70-71 find support, for example, in Table 1, on page 26, lines 1-7.

New claims 35-36, 54-55 and 72-73 find support, for example, in Table 1, on page 26, lines 10-14; and on page 18, lines 1-17.

New claim 37, 50 and 68 find support, for example, on page 43, line 8 through page 44, line 6.

New claims 38 and 56 find support, for example, in claim 7 as originally filed; on page 15, line 24 through page 16, line 2 and in Figure 7; on page 39, line 26 through page 40, line 22; and on page 51, lines 1-24.

New claims 39 and 57 find support, for example, in claim 9 as originally filed.

New claims 40 and 58 find support, for example, in claim 10 as originally filed.

New claims 41 and 59 find support, for example, on page 51, lines 10-11.

New claims 42 and 60 find support, for example, on page 24, lines 3-10.

New claims 43 and 61 find support, for example, on page 34, line 22 through page 35, line 22.

New claims 45-46 and 63-64 find support, for example, on page 35, lines 22-31.

New claims 47 and 65 find support, for example, on page 15, lines 24-31 and in Figure 7; and on page 51, lines 4-10 and 23-24.

New claims 48-49 and 66-67 find support, for example, in Table 2 on page 51, lines 17-20.

No new matter is added by the present amendments, and the Examiner is respectfully requested to enter them.

Amendments to the Specification

The Substitute Sequence Listing is amended to include the sequence in paragraph **[0090]** on page 34, line 14 as SEQ ID NO:298. Further changes to the previously submitted Sequence Listing include 1) modification to the description of the oligonucleotide of SEQ ID NO:49 to reflect the stimulatory CpG-ODN description in the Specification on page 47, lines 20-26; 2) a Feature added to SEQ ID NO:50 describing the phosphorothioate backbone to distinguish this sequence from SEQ ID NO:28; 3) modification to the description of the peptide antigen for the Artificial Sequence in SEQ ID NO:51; 4) addition of "dinucleotide" to the description of the Feature for SEQ ID NOS:53-56; 5) modification to the description of the nucleotide indicated by "n" as "i", rather than "Inosine" to conform to the symbol use in Table 2, Appendix 2 of WIPO Standard ST.25 for SEQ ID NOS:117-148 and 231-262; and 6) deletion of the extraneous Feature from SEQ ID NO:231.

The Substitute Sequence Listing is also amended to include the sequence for the pVAX1 vector as published on the Invitrogen website (attached as Exhibit A). The Specification on page 51 and new claims 31 and 32 include the sequence identifier (SEQ ID NO:297) for this sequence. The sequence for the pVAX1 vector presently available on the Invitrogen website has not changed since the February 10, 2005 filing date of the application.

Applicants request entry of this amendment in adherence with 37 C.F.R. §§1.821 to 1.825. This amendment is accompanied by a floppy disk containing the above named sequences, SEQ ID NOS:1-298, in computer readable form, and a paper copy of the sequence information which has been printed from the floppy disk.

The information contained in the computer readable disk was prepared through the use of the software program "PatentIn" and is identical to that of the paper copy.

No new matter is added by the present amendments, and the Examiner is respectfully requested to enter them.

Rejection under 35 U.S.C. § 112, first paragraph, enablement requirement

The Examiner rejected claims 7-10 and 25-30 under 35 U.S.C. § 112, first paragraph, as allegedly not enabled. To the extent that the present rejection applies to the amended claims, Applicants respectfully traverse.

The test of enablement is whether one reasonably skilled in the art could make or use the invention from the disclosures in the patent coupled with information known in the art without undue experimentation. *United States v. Telectronics, Inc.*, 857 F.2d 778, 785, 8 USPQ2d 1217, 1223 (Fed. Cir. 1988). A patent need not teach, and preferably omits, what is well known in the art. *In re Buchner*, 929 F.2d 660, 661, 18 USPQ2d 1331, 1332 (Fed. Cir. 1991); *Hybritech, Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1384, 231 USPQ 81, 94 (Fed. Cir. 1986). The fact that experimentation may be complex does not necessarily make it undue, if the art typically engages in such experimentation. *In re Certain Limited-Charge Cell Culture Microcarriers*, 221 USPQ 1165, 1174 (Int'l Trade Comm'n 1983). *See also, In re Wands*, 858 F.2d at 737, 8 USPQ2d at 1404. The test of enablement is not whether any experimentation is necessary, but whether, if experimentation is necessary, it is undue. *In re Angstadt*, 537 F.2d 498, 504, 190 USPQ 214, 219 (CCPA 1976).

Here, amended claim 7 is directed to a ***modified*** pVAX1 ***vector*** (SEQ ID NO:297), wherein the specific nucleotide changes made to the vector as set forth in Table 2 on page 51 of the specification are recited in the claim. Applicants have produced and demonstrated

the therapeutic efficacy of the vector set forth in claim 7; it is named pBHT1. *See, e.g.*, page 15, line 24 through page 16, line 2, Figure 7; and page 51, lines 1-24 of the specification.

New claim 37 is directed to a ***modified*** nucleic acid ***vector***, modified according to the expressly recited steps of (a) providing an unmodified vector with a CpG dinucleotide within a motif that is 5' purine-pyrimidine-C-G-pyrimidine-pyrimidine-3'; and (b) substituting the cytosine in the CpG dinucleotide to a non-cytosine in the motif to produce a modified nucleic acid vector that induces a reduced degree of immunostimulation in comparison to the unmodified nucleic acid vector. Applicants' specification teaches those of skill in the art how to identify the immunostimulatory CpG dinucleotide in the 5'-Purine-Pyrimidine-[X]-[Y]-Pyrimidine-Pyrimidine-3' hexamer motifs and to change the cytosine in the CpG dinucleotide. *See, e.g.*, page 39, line 26 through page 40, line 22. Applicants have reduced to practice the pBHT1 vector, which was made according to steps recited in the claims, and demonstrated its therapeutic efficacy. *See, e.g.*, page 15, line 24 through page 16, line 2, Figure 7; and page 51, lines 1-24 of the specification.

In view of the teachings in the specification for preparing and modifying the claimed vectors, the demonstration of the therapeutic efficacy of a modified vector produced according to the steps set forth in claim 37 and having the specific nucleotide changes set forth in claim 7, Applicants respectfully maintain that the specification teaches those of skill how to make and use the claimed modified vectors without undue experimentation and with a reasonable expectation of success. Accordingly, the Examiner is respectfully requested to withdraw this rejection.

Rejection under 35 U.S.C. § 112, first paragraph, written description requirement

The Examiner rejected claims 7-10 and 25-30 under 35 U.S.C. § 112, first paragraph, as allegedly failing to comply with the written description requirement. To the extent that the present rejection applies to the amended claims, Applicants respectfully traverse.

According to M.P.E.P. § 2163.02, to satisfy the written description requirement, an applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. *Vas-Cath, Inc. v. Mahurkar*, 935 F.2d

1555, 1563-64, 19 USPQ2d 1111, 1117 (Fed. Cir. 1991). An applicant shows possession of the claimed invention by describing the claimed invention with all of its limitations using such descriptive means as words, structures, figures, diagrams, and formulas that fully set forth the claimed invention. *Lockwood v. American Airlines, Inc.*, 107 F.3d 1565, 1572, 41 USPQ2d 1961, 1966 (Fed. Cir. 1997). Possession may be shown in a variety of ways including description of an actual reduction to practice, or by showing that the invention was "ready for patenting" such as by the disclosure of drawings or structural chemical formulas that show that the invention was complete, or by describing distinguishing identifying characteristics sufficient to show that the applicant was in possession of the claimed invention. *See, e.g., Regents of the University of California v. Eli Lilly*, 119 F.3d 1559, 1568, 43 USPQ2d 1398, 1406 (Fed. Cir. 1997); *Amgen, Inc. v. Chugai Pharmaceutical*, 927 F.2d 1200, 1206, 18 USPQ2d 1016, 1021 (Fed. Cir. 1991). The subject matter of the claim need not be described literally (*i.e.*, using the same terms or *in haec verba*) in order for the disclosure to satisfy the description requirement. Furthermore, a patent need not teach, and preferably omits, what is well known in the art. *In re Buchner*, 929 F.2d 660, 661, 18 USPQ2d 1331, 1332 (Fed. Cir. 1991); *Hybritech, Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1384, 231 USPQ 81, 94 (Fed. Cir. 1986). M.P.E.P. § 2164.

Here, Applicants have described and reduced to practice a pVAX1 vector (SEQ ID NO:297) modified to have a G at nucleotide positions 784, 1161, 1218, 1831, 1876, 1942, 1966 and 1999; and A at nucleotide positions 1264, 1337, 1829, 1874, 1940 and 1997; and a T at nucleotides 1963 and 1987, as set forth in claim 7. *See, e.g.*, page 15, lines 24-31 and Figure 7; and page 51, lines 1-24.

Applicants have also described and reduced to practice a nucleic acid vector made by the process of (a) providing an unmodified vector with a CpG dinucleotide within a motif that is 5' purine-pyrimidine-C-G-pyrimidine-pyrimidine-3'; and (b) substituting the cytosine in the CpG dinucleotide to a non-cytosine in the motif to produce a modified nucleic acid vector that induces a reduced degree of immunostimulation in comparison to the unmodified nucleic acid vector. *See, e.g.*, page 15, lines 24-31 and in Figure 7; on page 39, line 26 through page 40, line 22; and on page 51, lines 1-24. The exemplified embodiment is the pBHT1 vector, and those of

skill would readily recognize the general applicability of the process steps for producing a modified nucleic acid vector with reduced immunostimulatory properties.

Therefore, Applicants respectfully submit that a person of skill would recognize that Applicants have conveyed possession of the claimed vectors commensurate in scope with the claims. Accordingly, the Examiner is respectfully requested to withdraw this rejection.

Rejections under 35 U.S.C. § 102

Martin-Orozco, *Intl Immunol* (1999) 11/7:1111-1118 ("Martin-Orozco")

The Examiner has rejected claims 7-9 and 28 under 35 U.S.C. § 102(b) as allegedly anticipated by Martin-Orozco. To the extent that this rejection applies to the present claims, this rejection is respectfully traversed.

As the Examiner appreciates, anticipation requires that the cited reference disclose each and every element of the claimed invention, either expressly or inherently. M.P.E.P. § 2131.

Here, Martin-Orozco does not disclose or suggest a pVAX1 vector (SEQ ID NO:297) modified to have a G at nucleotide positions 784, 1161, 1218, 1831, 1876, 1942, 1966 and 1999; and A at nucleotide positions 1264, 1337, 1829, 1874, 1940 and 1997; and a T at nucleotides 1963 and 1987, as set forth in claim 7. Martin Orozco also does not disclose or suggest a nucleic acid vector made by the process of (a) providing an unmodified vector with a CpG dinucleotide within a motif that is 5' purine-pyrimidine-C-G-pyrimidine-pyrimidine-3'; and (b) substituting the cytosine in the CpG dinucleotide to a non-cytosine in the motif to produce a modified nucleic acid vector that induces a reduced degree of immunostimulation in comparison to the unmodified nucleic acid vector.

The Examiner alleges that Martin-Orozco discloses the plasmid pUC19 containing the hexamer ACGTTC, but this hexamer is ***not*** a 5' ***purine-pyrimidine***-C-G-pyrimidine-pyrimidine-3' motif. Instead, Martin Orozco discloses identifying the 5' ***purine-purine***-C-G-pyrimidine-pyrimidine-3' "AACGTT" ***in an oligodeoxynucleotide*** ("ODN") and changing it to "AAGGTT." *See*, Martin-Orozco at page 1112, column 1. Martin-Orozco does not identify any immunostimulatory hexamer motif ***in the pUC19 plasmid***, much less modify it.

In view of the forgoing, Martin-Orozco does not disclose or suggest each and every element of the claimed nucleic acid vector compositions. Accordingly, the Examiner is respectfully requested to withdraw this rejection.

U.S. Patent No. 6,225,292 ("Raz")

The Examiner has rejected claims 7-9 and 28 under 35 U.S.C. § 102(b) as allegedly anticipated by Raz. To the extent that this rejection applies to the present claims, this rejection is respectfully traversed.

Raz does not disclose or suggest a pVAX1 vector (SEQ ID NO:297) modified to have a G at nucleotide positions 784, 1161, 1218, 1831, 1876, 1942, 1966 and 1999; and A at nucleotide positions 1264, 1337, 1829, 1874, 1940 and 1997; and a T at nucleotides 1963 and 1987, as set forth in claim 7. Raz also does not disclose or suggest a nucleic acid vector made by the process of (a) providing an unmodified vector with a CpG dinucleotide within a motif that is 5' ***purine-pyrimidine***-C-G-pyrimidine-pyrimidine-3'; and (b) ***substituting*** the cytosine in the CpG dinucleotide to a non-cytosine in the motif to produce a modified nucleic acid vector that induces a reduced degree of immunostimulation in comparison to the unmodified nucleic acid vector.

In fact, Raz does not disclose or suggest identifying any immunostimulatory motif in a vector and modifying it. Instead, Raz discloses co-administering a polynucleotide comprising the immunoinhibitory hexamer motif 5' ***purine-purine***-Y-Z-pyrimidine-pyrimidine-3'. Raz discloses that their method of co-administering a polynucleotide containing an immunoinhibitory motif avoids the need for extensive reengineering of recombinant expression vectors to eliminate immunostimulatory nucleotide sequences ("ISS-ODN"). *See*, column 2, lines 6-10 of Raz. Raz also discloses that a particular advantage of co-administering a polynucleotide containing an immunoinhibitory oligonucleotide ("I-ON") is that the I-ON can be used to target ISS-ODN in any ISS-ODN containing recombinant expression vector whether or not the nucleotide composition of the vector is known. *See*, column 2, lines 60-66 of Raz.

In view of the forgoing, Raz does not disclose or suggest each and every element of the claimed nucleic acid vector compositions. Accordingly, the Examiner is respectfully requested to withdraw this rejection.

U.S. Patent No. 6,610,661 ("Carson")

The Examiner has rejected claims 7-9 and 28 under 35 U.S.C. § 102(e) as allegedly anticipated by Carson. To the extent that this rejection applies to the present claims, this rejection is respectfully traversed.

Carson does not disclose or suggest a pVAX1 vector (SEQ ID NO:297) modified to have a G at nucleotide positions 784, 1161, 1218, 1831, 1876, 1942, 1966 and 1999; and A at nucleotide positions 1264, 1337, 1829, 1874, 1940 and 1997; and a T at nucleotides 1963 and 1987, as set forth in claim 7. Carson also does not disclose or suggest a nucleic acid vector made by the process of (a) providing an unmodified vector with a CpG dinucleotide within a motif that is 5' ***purine-pyrimidine***-C-G-pyrimidine-pyrimidine-3'; and (b) substituting the cytosine in the CpG dinucleotide to a non-cytosine in the motif to produce a modified nucleic acid vector that induces a reduced degree of immunostimulation in comparison to the unmodified nucleic acid vector.

In fact, Carson also does not disclose or suggest identifying any immunostimulatory motif in a vector ***and modifying it for a reduced degree of immunostimulation***. Instead, Carson discloses identifying a polynucleotide comprising the immunostimulatory hexamer motif 5' ***purine-purine***-C-G-pyrimidine-pyrimidine-3' (ISS-PN). *See, e.g.*, Carson at column 2, lines 37-43; and at column 7, lines 22-26 and lines 58-65. Carson states that their invention is directed to combining a polynucleotide containing an immunostimulatory motif (ISS-PN) with an immune modulatory molecule (IMM) ***to synergistically boost the magnitude of the host immune response*** against an antigen to a level greater than the host immune response to either the IMM or ISS-PN alone. *See*, Carson at column 1, lines 53-57. Carson is clearly not seeking to produce a modified nucleic acid vector that induces a reduced degree of immunostimulation.

In view of the forgoing, Carson does not disclose or suggest each and every element of the claimed nucleic acid vector compositions. Accordingly, the Examiner is respectfully requested to withdraw this rejection.

Lipford, *Immunol* (2000) 101:46-52

The Examiner has rejected claims 7 and 25-29 under 35 U.S.C. § 102(b) as allegedly anticipated by Lipford. To the extent that this rejection applies to the present claims, this rejection is respectfully traversed.

Lipford does not disclose or suggest a pVAX1 vector (SEQ ID NO:297) modified to have a G at nucleotide positions 784, 1161, 1218, 1831, 1876, 1942, 1966 and 1999; and A at nucleotide positions 1264, 1337, 1829, 1874, 1940 and 1997; and a T at nucleotides 1963 and 1987, as set forth in claim 7. Lipford also does not disclose or suggest a nucleic acid vector made by the process of (a) providing an unmodified vector with a CpG dinucleotide within a motif that is 5'-***purine-pyrimidine***-C-G-pyrimidine-pyrimidine-3'; and (b) substituting the cytosine in the CpG dinucleotide to a non-cytosine in the motif to produce a modified nucleic acid vector that induces a reduced degree of immunostimulation in comparison to the unmodified nucleic acid vector.

In fact, Lipford also does not disclose or suggest identifying any immunostimulatory motif ***in a vector*** and modifying it. Instead, Lipford discloses studying the stimulation of T-cells *in vitro* with ***oligonucleotides*** comprising the immunostimulatory hexamer motif 5'-***purine-purine***-C-G-pyrimidine-pyrimidine-3'. In no instance does Lipford identify the hexamer motif 5'-***purine-pyrimidine***-C-G-pyrimidine-pyrimidine-3' as immunostimulatory. *See*, Table 1 on page 47 of Lipford. For example, the immunostimulatory motif identified in ODN 1668 is GACGTT, which is 5'-purine-purine-C-G-pyrimidine-pyrimidine-3'.

In view of the forgoing, Lipford does not disclose or suggest each and every element of the claimed nucleic acid vector compositions. Accordingly, the Examiner is respectfully requested to withdraw this rejection.

CONCLUSION

In view of the foregoing, Applicants believe all claims now pending in this Application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested.

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 415-576-0200.

Respectfully submitted,

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Attachments
JLW:jlw
61213363 v1

GACTCTTCGCGATGTACGGGCCAGATATACGCGTTGACATTGATTATTGACTAGTTATTAATAGTAATCA
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AGCAACGCGGCCTTTTTACGGTTCCTGGGCTTTTGCTGGCCTTTTGCTCACATGTTCTT

Exhibit A